Effectiveness of Fully Immersive Virtual Reality as a Pain and Distress Treatment Method as Compared to Standard Analgesic Treatments in Children Undergoing Painful Medical Procedures: a Systematic Review.

By

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Abstract

Effective pain and distress management remains a challenge for the paediatric population during medical procedures. Virtual Reality (VR) provides pain control by immersing an individual in a multisensory, 3-dimensional, computer-generated environment, offering a non-pharmacological way of pain reduction during invasive medical procedures. This research assessed the effect of VR distraction as a pain control method compared to standard pharmacological and non-pharmacological methods. A systematic review of the literature used PsycINFO, PubMed, and Google Scholar databases. Search terms included a randomised controlled trial (RCT), virtual reality/VR, augmented reality, child, paediatric, children, painful medical procedures, pain, and pain management. Studies were included in the systematic review if they used an RCT design, and the VR method of distraction was compared to a standard method of pain relief or no pain control at all. Participants aged 3 to 21 years old were undergoing painful medical procedures in hospital settings with standard care as pain management in the control groups and VR distraction in the experimental groups. Out of 123 records initially screened, nine papers were selected for the systematic review. They were assessed using the PEDro scale. The data collection was performed by the primary researcher, using Comprehensive Meta-Analysis Software Version 2 (CMA 2.0). VR demonstrated a statistically significant reduction in anxiety and pain in the experimental groups vs. control groups, with a large effect size (Hedges' $g = 1.30$, $SE = 0.38$).

A number of limitations included: VR is not applicable in children with severe head and hand burns or injuries. Motion sickness or nausea is a possible side effect of VR and can limit its clinical application. More research is needed to investigate the optimal dosage and sustainable efficacy of VR. Overall, VR distraction was effective compared to standard pain control methods and can be used during painful medical procedures to alleviate pain and anxiety in paediatric population.

Introduction and Literature Review

Repetitive painful medical procedures, such as burn wound dressing changes, lumbar punctures, bone marrow aspirations, chemotherapy, drug delivery systems, and injections, are necessary components of the management and treatment of adult and child cancer, injuries, burn wounds and other medical operations. The pain experienced during these procedures can be severe and intense and is often associated with significant anxiety and distress (Jeffs et al., 2014; Mott et al., 2007; Weisman, Bernstein, & Schechter, 1998). These adverse reactions can lead to the development of fear-avoidance behaviours compromising the very treatment that could help patients in the long term (von Baeyer, Marche, Rocha, & Salmon, 2004).

The International Association for the Study of Pain defined pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage' (Merskey, 1991). Pain is a subjective phenomenon, and a reaction to the pain stimulus is individualised (Young, 2005). Jay, Ozolins, Elliott, and Caldwell (1983) suggested that the ways pain is perceived are dependent on age, gender, previous pain experiences, and even cultural conditioning. The level of demonstrated anxiety, distress, and the range of external signs associated with these symptoms during painful medical procedures is higher in children compared to older groups of patients (Jay et al., 1983).

Children’s experience and memory of pain is the best predictor of future pain responses (Young, 2005). As a result of repetitive painful procedures, conditioned distress and fear become a serious concern for medical professionals and parents (Katz, Kellerman, & Siegel, 1980; Racine et al., 2016). Acquired anticipatory reactions of anxiety responses include vomiting, diarrhoea, irritability, insomnia, nightmares, aggression, depression, sudden urination, and even phobias (Jay, Elliott, Fitzgibbons, Woody, & Siegel, 1995; Wright, Stewart, & Finley, 2013). These symptoms interfere with the prescribed medical procedures

and in turn, compromise their results (Katz et al., 1980; von Baeyer et al., 2004). These symptoms may also compromise illness management and in extreme cases, can lead to an increased risk of morbidity and even mortality (Liberati et al., 2009). Therefore, adequate and efficient pain management is paramount to ensure that the anticipatory anxieties do not become habitual.

Painful medical procedures , such as bone marrow aspirations and wound dressing changes are often described as almost unbearable and distressing despite the liberal use of analgesics (Gold, Kim, Kant, Joseph, & Rizzo, 2006). The mean pain score for procedural pain levels in burn patients was reported as high as seven on a scale 1-10 in some studies (Carrougher et al., 2006; Schmitt et al., 2010). Several researchers have suggested that both pharmacological and cognitive-behavioural techniques, such as distraction, must be investigated and introduced to minimise pain scores during invasive procedures in children (Brown, Kimble, Rodger, Ware, & Cuttle, 2013; Windich-Biermeier, Sjoberg, Dale, Eshelman, & Guzzetta, 2007; Wolitzky, Fivush, Zimand, Hodges, & Rothbaum, 2005). Therefore, further investigation into various methods of pain management is essential for alleviating distress, discomfort, and decreasing side effects.

Pharmacological pain management techniques

Pharmacological pain management for children in New Zealand hospitals includes the application of topical anaesthetics, ethyl chloride spray, and sucrose (Starship child health, 2017). Another self-administered agent used during painful medical procedures is Entonox (nitrous oxide 50% and oxygen 50%). Entonox is an inhaled agent that acts as an effective though temporary, pain relief method by providing effective pain relief and sedation without loss of consciousness (Healthcare UK, 2019). Although the described pain management agents can provide temporary pain relief during invasive procedures, they have their limitations and side effects that may include nausea, vomiting, dizziness, the potential for loss

of consciousness, troubled breathing, and swelling on skin among other symptoms (Starship child health, 2017). As reported by Zier and Doescher (2010), the application of several inhaled general anaesthetic agents, including nitrous oxide has been linked to electroencephalographic seizure activity. Seizure activities were present in children with and without a history of epilepsy or other types of seizure activity, suggesting inhaled general anaesthetic agents can be a potential cause of this complication in the paediatric population.

Procedural sedation and analgesia are another pharmacological method of pain management often used during painful medical procedures , such as dressing changes for burns, lumbar punctures, placement of a venous catheter, and bone marrow aspirations (Krauss, Krauss, & Green, 2014). This technique involves the use of sedatives or analgesic agents, such as intravenous fentanyl, midazolam, propofol, and ketamine. There are three typical phases of sedation – pre-sedation, sedation, and post-sedation. Sedation in these phases ranges from lighter to deeper stages of analgesia, depending on the type of the procedure. Deeper sedation is used during oncology procedures , such as bone marrow aspiration, radioactive investigations, and other painful or potentially frightening medical procedures that children must undergo as part of their treatment or diagnostic plan (Finley, 2001). As noted by Krauss et al. (2014), it is important to monitor the vital signs of the patient, using “pulse oximetry, electrocardiography, and blood-pressure measurement” as a core part of procedural sedation and safety enhancement. At shallower levels of sedation, a patient would usually maintain open airways and adequate respiration without additional medical assistance; however, at the deeper levels of sedation, the risk of airway obstruction and apnoea will increase (Krauss et al., 2014).

In addition to potential health implications, sedation includes a high economic cost, since the procedure involves not only the anaesthesia itself, but also trained personnel, access to hospital day beds, and monitoring equipment. A minimum of two experienced medical

staff are required for safe procedural sedation – usually, it will include a physician who provides the medical procedure and a nurse to monitor the vital signs of a patient. Medical personnel who apply this type of pain management must be able to "rescue" their patients if an unexpected adverse reaction occurs, which also requires resuscitation equipment (Edwards & Arthurs, 2011).

Although conventional pain management procedures are generally safe and effective when applied by trained personnel, they are associated with high costs and post-procedural complications. While some form of pain relief during invasive procedures is necessary, it is crucial to select easily employed pain management procedures that can provide a non-traumatic experience during operative and post-operative periods.

Alternative procedures and their limitations

Several methods have been developed to improve a child's ability to undergo a painful medical procedure without the use of sedation, including distraction, cognitive-behavioural therapy (CBT), educational play therapy, and hypnosis (Kenney & Milling, 2016; Uman, Chambers, McGrath, & Kisely, 2008). Distraction for the paediatric population involves redirecting the patient's attention from a painful stimulus toward a different event, such as watching a cartoon or a movie, deep breathing or blowing a pinwheel. This method stems from the premise that human brain has limited attentional resources, and therefore, any task that occupies some portion of human attention would leave less cognitive capacity to focus on the pain (Kenney & Milling, 2016) . Also, the way the pain is treated can be significantly modified by distraction altering subjective experience during painful procedures (Piira, Hayes, & Goodenough, 2002). Regional cerebral blood flow that occurs during painful medical procedures is reduced during distractive activities and the brain areas associated with pain 'such as the thalamus, insula, and anterior cingulate cortex', are less activated and thus produce fewer pain impulses (Windich-Biermeier et al., 2007).

Standard methods include age appropriate distracters such as books, watching videos, storytelling, music therapy, using a toy and breathing exercises (Mason, Johnson, & Woolley, 1999; Nguyen, Nilsson, Hellström, & Bengtson, 2010; Sinha, Christopher, Fenn, & Reeves, 2006; Uman et al., 2008). Studies that used music therapy and toy therapy as their methods of distraction demonstrated the effectiveness of these interventions during painful medical procedures (Nguyen et al., 2010; Sinha et al., 2006). Children in the experimental groups used earphones with their favourite music or played with the favourite toy. Children in the control groups did not use any music or toys. In these studies, self-reported pain levels were statistically lower in distraction groups than in control groups. Although these results showed that overall distraction could be an effective pain relief intervention, it was also noted that the age appropriate distractors should be combined with pharmacological methods of pain management for optimal results.

Some researchers studied the application of diversion techniques in reducing children's pain scores during lumbar punctures, venipunctures, burn wound dressing changes, and bone marrow aspirations (Katz et al., 1980; Mason, Johnson, & Woolley, 1999). Diversion techniques included reading books or watching movies. For example, a study by Mason et al. (1999) used interventions in which a parent read the child a short story or the child was watching a short film. This study showed statistically significant reduction in pain in the "reading a story with a parent" condition; however, the results were not statistically significant in the "watching a film" condition, suggesting that children may require guidance in attending to the distraction tasks effectively.

Although some studies demonstrated a statistically significant reduction in self-reported levels of pain and distress, results remained inconclusive. A systematic review by Uman et al. (2008) across 28 studies showed statistically significant reduction in self-reported pain and distress. However, behavioural and observer-reported measures of pain and distress across

the studies such as the Face, Legs, Activity, Cry, Consolability scale (FLACC), demonstrated that this method was not effective in reducing pain and distress in children during painful medical procedures. Similarly, Birnie et al. (2014) in her systematic review of distraction as a pain management strategy in paediatric needle-related procedures argued that although standard methods of distraction led to significant reduction in self-reported pain, there was no evidence to support their efficacy for behavioural measures of pain.

CBT is another example of psychological interventions for pain. CBT combines a variety of procedures intended to improve a patient's ability to cope with pain and to modify their appraisal of the painful experience. There are several techniques used under the umbrella of CBT, such as 'relaxation, guided imagery, and coping self-statements', that often are combined into one multi-component treatment (Kenney & Milling, 2016).

A study by Jay et al. (1995) compared the efficacy of CBT versus general analgesia (GA) as a pain relief method in paediatric cancer patients. The results indicated that children in the CBT condition demonstrated more distress during the treatment and no differences were found in parental and patients' preferences for CBT versus GA use. On the contrary, the results of Jay et al. (1991) study demonstrated efficacy of CBT in reducing procedural pain in children. It produced statistically significant results in such outcome measures as behavioural stress, self-reported pain and anxiety and pulse rate.

Perhaps the most comprehensive meta-analysis of the efficacy of CBT was conducted by Uman et al. (2008). This study analysed the results of six randomised controlled trials (RCTs) involving 277 paediatric patients from two to 19 years of age. The combined results of the analysis showed a statistically significant reduction in behavioural, but not in self-reported levels of pain and distress. Thus, the combined results of the analysis illustrated the efficacy of CBT in reducing some, but not all, measures of pain and distress in paediatric population during painful medical procedures (Uman et al., 2008).

Another method for helping children to undergo a painful medical procedure is educational play therapy (i.e., use of medical toys, sound and interactive books, and non-procedural talk) as a means of explaining the process (Delany & Conwell, 2012; Pressdee, May, Eastman, & Grier, 1997). This approach is based on findings that children may experience less anxiety and distress if they are well prepared and informed about the procedure (Szeszak et al., 2016). The use of educational play therapy helps to prepare and to educate children about the procedure in an interactive way. During the consultation, a therapist can answer any questions that a child or their parent may have in relation to the upcoming procedure. They are also able to correct any misconceptions concerning the expected procedure. The consultations help the child and their parents to understand the procedure better and to allay possible fears associated with it, thus potentially reducing possible anticipatory anxiety and distress (Pressdee et al., 1997)).

Although some studies reported high success rates when using this intervention, their clinical utility can be low due to the high cost, shortage of appropriately trained personnel and insufficient time to offer the appropriate level of preparation (Szeszak et al., 2016). Moreover, evidence to demonstrate the effects of educational play therapy within the hospital context is contradictory. Some studies have found no evidence of the therapeutic effects of the play intervention and conversely, have suggested that the preliminary information about upcoming medical procedures led to increased questioning and overall anxiety level in the patients (Hartman, Bena, McIntyre, & Albert, 2009).

In a systematic review conducted by He, Zhu, Chan, Klainin-Yobas, and Wang (2015), six studies examined the effectiveness of a therapeutic play intervention in paediatric population during an invasive procedure. The outcome measures of perioperative and postoperative anxiety, pain, and negative behaviour were heterogeneous. Their designs and timing varied greatly across all six studies. The results yielded by these studies were

conflicting and inconsistent. The outcome of this review suggested that current evidence of the effects of play intervention on pain and distress was inconclusive and further research using more rigorous experimental designs were needed.

A final strategy identified that has been used to alleviate pain during aversive medical procedures is hypnosis. This method has been proposed as the most effective pain management intervention in children on the premise that children overall were more hypnotically responsive compared to adults (Wild & Espie, 2004). Hypnosis uses direct suggestion to a patient to reduce their perception of pain and to modify their thinking and behaviour (Ramírez-Carrasco, Butrón-Téllez Girón, Sanchez-Armass, & Pierdant-Pérez, 2017). It has been widely and often successfully applied across a number of painful paediatric procedures, such as bone marrow aspiration, lumbar punctures and dental procedures (Kuttner, Bowman, & Teasdale, 1988; Liossi & Hatira, 2003; Ramírez-Carrasco et al., 2017). Smith, Barabasz, and Barabasz (1996) used hypnosis and distraction methods of pain management in groups of high and low hypnotizable children subjected to invasive medical procedures. Hypnosis was compared to distraction as a method of pain and anxiety control. For distraction, parents were instructed to play with children using a toy of their choice. The research argued that hypnosis was more effective in reducing pain and distress perception in children during painful medical procedures compared to other psychological methods of pain management. The results suggested that the subjective pain and anxiety were significantly lower in high hypnotizable children. However, the low hypnotizable group showed significantly better results in distraction intervention.

Several studies have reported statistically significant reductions in pain and anxiety during hypnosis (Kuttner et al., 1988; Richardson, Smith, McCall, & Pilkington, 2006). The qualitative differences in subjective pain ratings between high and low hypnotizable patients though supported the notion that this intervention was not suitable for every child and the

results were largely dependent on the subjective responses to the hypnotic process. The summary of the systematic review conducted by Wild and Espie (2004) also produced inconclusive results for the efficacy of hypnosis intervention and indicated generally poor methodological quality of research.

Virtual reality

Recent research has suggested that children may respond better to interactive means of distraction (e.g., playing a video game) as opposed to passive techniques, such as watching a video (Wohlheiter & Dahlquist, 2013). Current technological advancement has generated significant interest in VR as a potential distraction method for children undergoing painful medical procedures.

There are two main categories of VR systems: immersive and non-immersive. Non-immersive VR provides the user with a computer-generated environment without full presence in the virtual world. The interaction with the digital content on the screen in non-immersive VR systems happens with the use of various input devices, such as a mouse, keyboard, and joystick (Nilsson, Finnström, Kokinsky, & Enskär, 2009).

In contrast to this, immersive VR uses computer-generated technology to immerse a person in a three-dimensional, multisensory environment with complete isolation from the real world (Kenney & Milling, 2016). This ‘immersion’ is achieved through real-time computer graphics, head-mounted displays (HMD), earphones, and other sensory input, which makes a person an active participant inside a three-dimensional computer-generated realm (Lambert, Matthews, Hicks, Boran, & Devane, 2013). Ability to navigate in immersive VR is achieved using a joystick or wand (Kenney & Milling, 2016). The HMD helmet consists of a tracking device, display optics, and two screens – one for each eye. It delivers information to a computer about an individual’s head position, which generates visual images on the headset. The images correspond to the orientation of the user’s head and the direction

in which the user is looking, within a 3D world (Rothbaum & Hodges, 1999). The headset eliminates the patient's entire view of their in-vivo surroundings replacing it with the visual simulation of the virtual world. The visuals on the screen are typically delivered via an HDMI cable connected to a computer (Jeffs et al., 2014). The three distinctive characteristics of the virtual reality intervention are interaction, navigation, and immersion that result in the sense of 'presence' inside the virtual world.

The theory of VR distraction.

VR as a distraction method of pain management is based on the premise that it occupies a significant part of conscious attention leaving fewer cognitive resources to evaluate and process painful impulses during otherwise stressful and painful procedures. The brain receives information about pain stimuli from the pain receptors through neural signals. A patient's brain requires attention to process this information and there is only a limited amount of information a brain can attend to and process at any given time (Schmitt et al., 2010). VR draws heavily upon conscious awareness by flooding the brain with information from multiple senses leaving limited capacity for processing pain signals. This process results in spending less time thinking and paying attention to pain (Hoffman et al., 2006).

Research into the effectiveness of VR as a pain and anxiety intervention in adults has demonstrated promising results (Cardoş, David, & David, 2017; Dascal et al., 2017; Malloy & Milling, 2010).The systematic review conducted by Malloy and Milling (2010) yielded the mean weighted effect size of -.94. The results further indicated that the average patient who used VR as a distraction method during invasive procedures showed more improvement than about 83% of the patients who underwent conventional methods of pain management. Similarly, a systematic review conducted by Dascal et al. (2017), addressed the use of VR in three general areas: cognitive and motor recovery, eating disorders, and pain distraction. The

studies included in this systematic review were heterogeneous and applied different designs and methods. The mean weighted effect size was -.87 indicating the clinical efficacy of VR.

Although the medical applications of VR in the paediatric population are still being explored, some studies have explored the effectiveness of VR in treating anxiety in children during chemotherapy. In the RCT conducted by Gershon, Zimand, Pickering, Rothbaum, and Hodges (2004), children with cancer, aged seven to nineteen, required venous port access. They were randomly assigned to a virtual reality intervention group, a non-VR distraction, and a treatment "as usual" with no distraction group. Pain and anxiety measures during the procedure were obtained from children, their parents, and unblinded nurses. Results found significant reduction in pain and anxiety in the VR group compared to both non-VR and treatment with no distraction groups. These findings suggested that VR might be applied as an effective therapeutic method of distraction during chemotherapy and other similar procedures that require venous port access.

Other research has demonstrated the successful application of VR, as a distraction and analgesic method, during invasive procedures such as burn-care and dressing changes (Das, Grimmer, Sparnon, McRae, & Thomas, 2005; Hoffman, Patterson, Carrougher, & Sharar, 2001; Hoffman et al., 2019; Semas, 2018). For example, Kipping, Rodger, Miller, and Kimble (2012b) assessed the effect of VR on acute pain intensity reduction in adolescents aged between 11 and 17. This study used an RCT design with 41 adolescents assigned to two groups. The VR group used VR as a method of distraction during burn wound dressing change and the Control group used standard means of distraction, such as TV, music, stories, and access to caregivers. The results showed a statistically significant reduction in pain in the VR group compared to the standard distraction group. These findings suggested that a hospital-friendly VR device might be a more effective method of pain reduction during painful medical procedures compared to conventional distraction techniques.

The research conducted by Steele et al. (2003) reported the successful application of VR in an adolescent patient with cerebral palsy undergoing physiotherapy after a multi-level surgery. During his physiotherapy treatments, the patient used VR in the experimental condition for half of each session. The control condition during the other half of each session used only epidural local anaesthetic and opioid mixture as a pharmacological method of intervention. The order of the experimental and control conditions was randomised. The results of this case study showed a statistically significant difference between pain reductions in the experimental versus the control condition. The overall decrease in pain in the VR condition compared to non-VR condition was 41.2%. The parental evaluation of anxiety and distress scores showed a statistically significant reduction in anxiety and increased motivation to undergo post-surgical physiotherapy when the patient used VR during their treatments suggesting that this method may be more effective compared to standard pharmacological means typically used in post-surgical treatment and recovery. These results are consistent with other studies that have demonstrated consistent reduction in pain in children undergoing painful medical procedures using VR as a distraction method (K. Miller, Rodger, Bucolo, Greer, & Kimble, 2010; Nilsson et al., 2013; Sharar et al., 2008; Walker et al., 2014).

Similar to the other therapeutic methods, VR simulations can be tailored for certain types of procedures (e.g., a Snow World game was developed for burn wound dressing changes; (Hoffman et al., 2004)). However, unlike other distractive methods, VR is the only known technique that allows a patient to immerse, navigate, and interact inside a tailored computer-generated real-time world. VR can be seen as an ideal distractive method for children undergoing painful medical procedures because it allows a patient to immerse into a lifelike experience with a complete sense of presence.

Unfortunately, research on the effectiveness of VR as a pain control approach in paediatric patients is limited. The majority of existing research has been conducted with the

adult population only, and generally included a small number of participants. Within the recent 10-15 years, the number of controlled trials on the effects of VR as a distraction method for managing pain has increased. The purpose of this systematic review was to analyse all of the controlled studies investigating the effectiveness of this type of intervention during various painful medical procedures in paediatric population, and to compare it to other, more conventional methods, both pharmacological and non-pharmacological.

Aim and hypothesis of the current study

The aim of this study is to quantify the effect of virtual reality as a distraction method when used during painful medical procedures amongst the paediatric population (aged 3-21) in hospital settings, compared to traditional methods of analgesia. The research was designed as a subgroup analysis of all randomised controlled trials that involved VR as their method of distraction to compare its effectiveness to the conventional pharmacological and non-pharmacological methods of pain relief, as measured by clinical outcome measures of pain. It is hypothesised that children who receive VR, as a method of distraction during invasive procedures will show lower levels of pain and distress compared to their non-VR counterparts. The null hypothesis is that VR is no more effective as a pain and anxiety management method for invasive medical procedures compared to conventional pharmacological and non-pharmacological pain management techniques.

Research Design and Methods

The main objective of this systematic review was to determine how effective VR based intervention would be compared with the other types of pain-reducing interventions during painful medical procedures. This question was answered using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). The aim of a systematic review is to collate all empirical evidence based on pre-specified

eligibility criteria using specific methods to minimise bias and to provide reliable answers to the specified research questions. The PRISMA guidelines include a 27- item checklist relating to items considered essential for transparent reporting and standardised writing of systematic reviews. The items contain explicit and reproducible steps to inform and conduct data searching, such as description of all information sources, description of the eligibility criteria and study selection process, methods of data extraction and assessment of risk of bias, and, qualitative and quantitative synthesis of the results from the selected studies (Liberati et al., 2009).

Inclusion/Exclusion Criteria

The inclusion criteria for the review were as follows:

1. Participants had to include children of both sexes and all ethnicities, aged between three and 21 years. The age range between three and 21 was chosen because a child must be at least three years old to be able to communicate effectively and to rate their level of distress and pain, and must be no older than 21 years of age to be included in the paediatric category (Williams et al., 2012).
2. In the experimental groups, the intervention had to include immersive VR as the pain and distress treatment methods, and this must have been provided during painful medical procedures.
3. The control group interventions were required to use standard pharmacological or non-pharmacological methods of analgesia, or no-treatment during painful medical procedures.
4. The outcomes of the interventions had to assess the effectiveness of VR distraction as a method of pain control as compared to standard methods of treatment. Pain intensity as the main outcome had to be assessed using standard self-reported measurement scales (VAS, FACES, STAIC) and observer-reported ratings (FLACC).

5. The studies needed to use an RCT design to compare treatment effects.
6. The studies had to be published in peer-reviewed, English language journals. The date of the publication was not one of the key inclusion criteria. This is a relatively new area of investigation in the field of psychology and related sciences; therefore, any related research irrespective of the year of publication may be relevant. The cut-off date for the search for any related published studies was March 2019 as this was the date when this systematic review was conducted. Funding for the professional translation of manuscripts was not available, meaning that only studies published in English were able to be included.

Studies were excluded from the systematic review if they were observational studies; qualitative or non-randomised controlled trial design studies; if the intervention did not include VR distraction as a chosen pain management method or VR was not used during painful medical procedures, or if participants were outside of the age range. Finally, studies that used audio-visual glasses for passive observation of the material that did not provide full interaction and immersion into the virtual world, were not considered as VR examples, and were excluded from this systematic review.

Clinical Outcome Measures of Pain

Clinical outcome measures of pain depicted in this systematic review included standard pain measurement scales, such as Wong Baker face pain scale (FACES), Visual Analogue Scale (VAS), the Face, Legs, Activity, Cry, Consolability scale (FLACC), Spielberger State-Trait Anxiety Inventory for Children (STAIC), and Graphic Rating Scale (GRS).

Self-report measurements of pain, such as Wong-Baker FACES, as well as VAS, have been demonstrated to be valid and reliable measures of pain assessment in children (Tomlinson, von Baeyer, Stinson, & Sung, 2010; Wong & Baker, 2001). Another self-report

questionnaire designed to measure procedural anxiety in children was the STAIC (Spielberger, 1973). It was successfully used in both clinical and research practice, and the reliability and validity of this scale have been demonstrated in multiple research studies (Delvecchio, Cavallina, Di Riso, & Mazzeschi, 2018; Hagtvet & Sipos, 2004; Psychountaki, Zervas, Karteroliotis, & Spielberger, 2003).

The FACES pain scale was developed for use in younger children, children who are preverbal, or those who have cognitive impairments. It is a popular self-report measure of pain intensity in paediatric acute, recurrent, or procedural pain because it is less abstract and easier-to-use than other available self-report measures in paediatric settings (Tomlinson et al., 2010).

The fact that these pain measurement scales are commonly used within clinical settings and among the included studies, determined the choice for this statistical analysis. However, variation in the use of these measurement scales was found in some of the selected studies. For example, the Adolescent Paediatric Pain Tool (APPT) utilised a 100-mm line known as the Word Graphic Rating Scale (WGRS). This was used in the Jeffs et al. (2014) study. Pain scores on this rating scale were from zero (no pain) to 100 (worst pain).

The FLACC scale measures procedural and postoperative pain in children aged two months to seven years of age. It has been used widely in hospital settings as a pain measurement scale during various painful medical procedures. This measure has shown a high level of clinical usefulness (Dorfman, Schellenberg, Rempel, Scott, & Hartling, 2014). Unlike self-report pain measurement scales , such as the VAS, FACES, and APPT, FLACC allows a child’s pain to be evaluated by the child’s caregiver and/or medical staff where required. The external rating of pain scores is based on specific objective signs exhibited by a paediatric patient. However, since pain is a subjective estimate, only those studies that used

self-report measurements of pain in addition to FLACC were selected for the systematic review.

Operational Definitions

For the purpose of this systematic review, VR was defined as a technological device that provides full auditory and visual interaction and immersion into the virtual world. Augmented reality is often used as a variation of VR and is described as a composite view consisting of the overlaid computer-generated image on the physical world of the viewer (Mott et al., 2007). Augmented reality was included in the analysis under the umbrella term of VR.

For the purpose of this systematic review, the definition of standard care during painful medical procedures included pharmacological types of distraction commonly used in hospital settings such as topical and oral analgesia, and non-pharmacological types of distraction such as caregiver distraction, reading, watching movies or being soothed.

Search Criteria

The systematic literature review was limited to three databases - PsycINFO, PubMed, and Google Scholar. This limitation was acceptable because all three databases are powerful web search engines and cover the necessary disciplines in which this type of research is likely to be undertaken. PsycINFO, PubMed, and Google Scholar were searched systematically by the primary researcher in March 2019. The search algorithm is presented in Table1.

Table 1. Search Algorithm for the Systematic Literature Review.

Database	Search	Terms used
Psycinfo	#1	'randomised controlled trial OR RCT', 'virtual reality OR VR OR augmented reality' AND 'child* OR paediatric OR children' AND 'painful medical procedures OR pain OR pain management'
Google Scholar	#2	'randomised controlled trial virtual reality OR VR', 'randomised controlled trial OR VR', 'painful medical procedures OR randomised controlled trial', 'virtual reality paediatric OR randomised controlled trial virtual reality children'
PubMed	#3	'randomised controlled trial OR RCT', 'virtual reality OR VR OR augmented reality' AND 'child* OR paediatric OR children' AND 'painful medical procedures OR pain OR pain management'

Study Selection

Study selection was undertaken in accordance with the PRISMA guidelines. The initial screening of the articles included the review of their titles and abstracts based on the stated inclusion and exclusion criteria. After the initial screening through titles and abstracts, a second screening stage was undertaken, in which I obtained the full texts of the studies that met the selection criteria in the first stage. These articles were further reviewed and analysed

in-depth for specific data and content. Additional studies were excluded during this process because they could not be classified as RCT despite the original search criteria results.

Quality Assessment Using PEDro Rating Scale.

The quality of the selected articles was assessed using the Physiotherapy Evidence Database (PEDro scale) (Physiotherapy Evidence Database, 2019).PEDro scale was developed to evaluate the quality of clinical trials. It was utilised as a method of quality assessment in this review because this scale is considered a valid measure of the methodological valuation of clinical trials (de Morton, 2009).The evaluation is based upon an 11-point scale to assess the quality of RCTs in systematic reviews and meta-analyses (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003).

The PEDro scale has assessed the strength of the selected studies in the areas of internal and external validity. It has also checked whether the statistical data were sufficient to make the results interpretable. The criteria were satisfied if the article clearly described the eligibility to participate in a study, provided random, double-blinded, and concealed allocation of the subjects; treated condition and outcome measures were identified, and between-group statistical comparison was provided (Maher et al., 2003). Each criterion of validity was clearly specified within each article and was awarded one point.

Data Collection Process

Statistical data was collected from pain measurement scales, such as VAS, FLACC, STAIC, FACES and GRS. A detailed description of these scales was provided earlier in the ‘Clinical Outcome Measures of Pain’ section of this review. The primary researcher retrieved these data independently from various tables, graphs, and the written content of the articles. Studies were evaluated for their effect size, p-value, Q-statistic, and heterogeneity. The effect size was calculated for each study included in the systematic review.

Summary Measures

Effect size.

The effect size quantified the magnitude of the difference in post pain between two groups – the VR and standard care group, divided by the pooled SD (Cohen's d). Cohen (2013), classified the magnitude of effect sizes as being small at .2, medium at .5, and .8 as large. Therefore, effect sizes for the systematic review were determined to be small, medium, large, or very large.

Standard deviations (SD) and confidence intervals (CI) were calculated for each individual study and a p-value of <0.05 was determined to be statistically significant at 95% CI. Negative scores in pain and anxiety measurements indicated a decrease in the symptoms, which equated to positive treatment outcome. Therefore, a negative effect size was indicative of a positive treatment effect.

Heterogeneity of the studies.

Cochran (1954) Q-statistic was used to assess heterogeneity between the studies, indicating presence versus the absence of between-studies variability. In the case where studies differ only by their sampling error, they are deemed homogeneous and a fixed-effect model can be used to calculate the overall effect size. By contrast, when heterogeneity is present, a random-effects model is a more appropriate method to estimate the total effect size (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006).

The Q-statistic was calculated by calculating the weighted sum of the squared deviations between each study effect and the overall effect across studies, with the contribution of each study weighted by its inverse variance method (Huedo-Medina et al., 2006). Based on a cut-off p-value, it determined whether these properties were significant or

not. The results of the Q-statistic were significant and there was evidence of true heterogeneity if the confidence limits did not contain a zero value. If the data indicated homogeneity between the studies, then they were considered similar. In the case of their heterogeneity, they were deemed dissimilar.

A shortcoming of the Q-statistics is that it does not inform us about the extent of true heterogeneity, only its statistical significance (Cornwell, 1993). Moreover, some researchers argued that the Q statistic has a low power to detect a true heterogeneity in the meta-analysis with a small number of studies (Higgins & Thompson, 2002; Huedo-Medina et al., 2006; Maeda & Harwell, 2016).

To overcome these shortcomings, new, interrelated indices to measure heterogeneity were proposed by Higgins and Thompson (2002). This systematic review will focus on just one of them – I-squared, because of its straightforward and easy interpretation. It quantifies the magnitude of heterogeneity between effect sizes by comparing their given Q-value to their expected value if they were homogeneous. The magnitude of heterogeneity was classified as low, medium, and high if I-squared percentages were around 25%, 50%, and above 75%, respectively (Higgins & Thompson, 2002).

Subgroup analysis.

The purpose of the subgroup analysis is to detect any variance in treatment effect (heterogeneity) across subgroups of clinical trials. Subgroup analysis plays an important role in the correct interpretation of the clinical trials' findings. If the results of the analysis demonstrate a consistent effect across different subgroups, then the treatment effect can be generalised regardless of the subgroup baseline factors. Significant heterogeneity may indicate that the treatment may be effective only in a certain subgroup of a population and may not benefit other subgroups in a similar way (Alosh et al., 2015).

The variance test was performed using subgroup analysis. Studies were grouped into three different models based on varying independent variables. The homogeneity of the studies was calculated as within- and between-studies variance. If the Q-value between the studies was significant, then the difference between the mean effect sizes of the subgroups of the individual studies was the result of more than just a chance.

R2 index as a proportion of the variance explained.

In addition to detecting variance in treatment effect across subgroups of clinical trials, it is important to quantify the strength of the impact of subgroup variables on effect size (X. Wang, Jiang, & Liu, 2017). The impact of a subgroup variable is described as the proportion of the variance explained by that variable. It is reported through R2 index that represents the proportion of the variance for a dependent variable explained by an independent variable.

Analysis of publication bias.

Each of the selected studies was drawn from peer-reviewed journals, which might raise concerns about publication bias. This type of bias is concerned with the studies that have been conducted but published selectively, based on their statistically significant outcomes. It is hypothesised that the studies with a statistically significant result would have a greater likelihood of publication when compared to studies that did not yield any statistically significant results (Orwin, 1983; Parmley, 1994; Strüver, 2016). Selective publication may lead to the inflated combined effect size of the published studies. Publication bias analysis would indicate a potentially biased study in the review, and would calibrate the estimate of the total effect size.

The presence of potential publication bias in this systematic review was assessed by building a funnel plot. A funnel plot is a scatter plot that indicates the relationships between the treatment effects and the measure of study size. In the absence of publication bias, it is

assumed that the larger studies are plotted near the centre (the mean effect size), and the smaller studies are symmetrically located on both sides, creating a funnel shape distribution. Deviation from the funnel shape can indicate publication bias or systematic heterogeneity (Egger, Smith, Schneider, & Minder, 1997).

Results

Study Selection

The initial search of three databases for RCTs revealed a total of 123 hits. PsycINFO yielded the highest number of results (50 hits); 41 records were identified through Google Scholar; and 32 records were identified through PubMed. Then these 123 records were further assessed for the presence of duplicates. Twelve duplicates were removed, and the remaining 111 records were screened. In total, 75 studies were excluded from the review because they did not meet the necessary inclusion criteria. The remaining 36 full-text articles were assessed for eligibility, and after screening them, only nine full-text studies remained for further evaluation. Most of studies were excluded because they were not classified as an RCT design.

The primary researcher conducted the initial screening of the studies independently. The main supervisor reviewed the remaining nine studies to confirm further whether the eligibility criteria had been met. Refer to Figure 1 for the flowchart of the selection process for the systematic review.

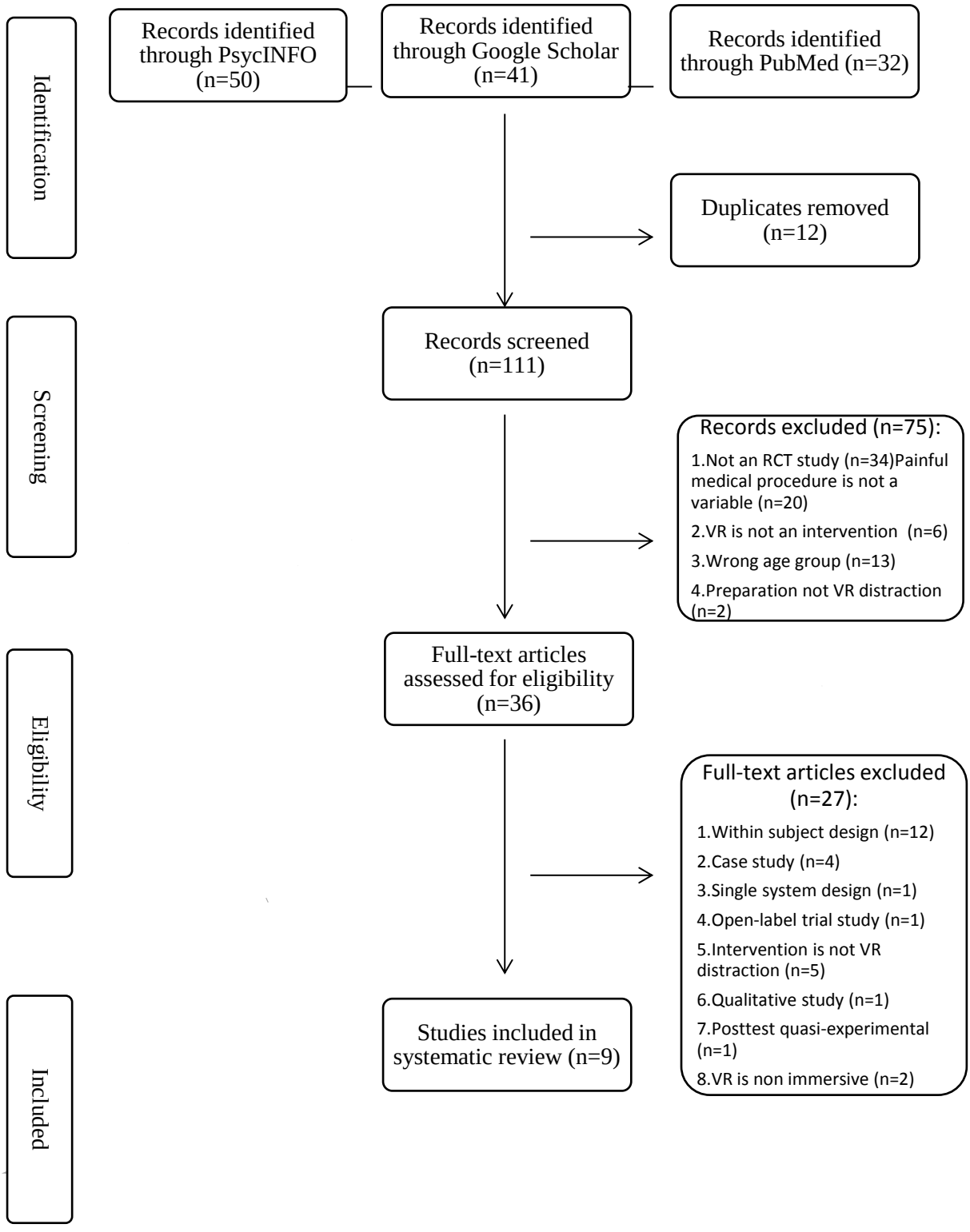

Figure 1. *PRISMA flow chart for study selection.*

Study Characteristics

The nine studies were all RCTs. Table 2 provides a summary of the selected articles, including the age range of the participants, the type of medical procedure, type of intervention, and clinical outcome measures.

Table 2. Characteristics of the Nine Studies Included in Systematic Review.

Study	Age	Study sample	Type of procedure	Type of VR	Measured outcomes	Type of intervention in Control group	Clinical outcome measures
Das et al. (2005)	5-18	14	Burn wound care	FI	Pain	Pharmacologic analgesia	FACES VAS
Gershon, Zimand, Pickering, Rothbaum, and Hodges (2004)	7-19	44	Port access	FI	Pain; anxiety	No distraction & non-pharmacological distraction	VAS
Gold et al. (2006)	8-12	20	IV placement	FI	Pain; anxiety	Pharmacologic analgesia	VAS; FACES; CASI
Hua, Qiu, Yao, Zhang, and Chen (2015)	4-16	65	Chronic wounds on lower limbs	FI	Pain; anxiety	Non-pharmacological distraction	FACES; VAS; FLACC
Jeffs et al. (2014)	10-17	18	Burn wound care	FI	Pain; anxiety	Pharmacologic analgesia	APPT; STAI
Kipping, Rodger, Miller, and Kimble (2012)	11-17	41	Burn wound care	FI	Pain	Non-pharmacological distraction	VAS; FLACC
Mott et al. (2007)	3-14	42	Burn wound care	AR	Pain; anxiety	Pharmacologic analgesia	FLACC; VAS;
Schmitt et al. (2010)	6-19	108	Burn wound care	FI	Pain	Pharmacologic analgesia	GRS
Wolitzky et al. (2005)	7-14	20	Port access	FI	Pain; anxiety; stress	Pharmacologic analgesia	VAS

VP=venipuncture; FI= fully immersive; NI=non-immersive; CASI= Childhood Anxiety Sensitivity Index; VAS=Visual Analogue Scale; FACES=the Wong-Baker FACES Pain Rating Scale(Wong & Baker, 2001); FLACC=Face, Legs, Activity, Cry and Consolability scale; CAS=colour Analogue Scale; FAS=Facial Affective Scale; APPT=Adolescent Paediatric Pain Tool; STAIC=State-Trait Anxiety Inventory; GRS=Graphic Rating Scale; AR=Augmented Reality

Measured outcomes.

Six out of nine selected studies evaluated subjective pain scores along with individual stress and/or anxiety levels. However, three studies measured pain outcomes only. Since the level of subjective pain immediately after the medical procedure is the primary clinical outcome, these studies were included in the systematic review alongside the others that used a variety of measurements to establish VR effectiveness in paediatric pain reduction.

Type of pain relief used in the control groups.

Interventions in the control groups in all nine studies included routine pharmacological analgesia or non-pharmacological distraction. Six out of nine selected studies employed some kind of pharmacological analgesia as their type of pain management in control groups. The other three studies used some kind of non-pharmacological pain relief method during invasive medical procedure.

In the trial conducted by Gershon et al. (2004) control group participants received no distraction or pain relief treatment representing how treatments for oncology patients during intravenous port access were typically conducted.

Study by Hua et al. (2015) employed standard methods of pain management for their control subjects, including the use of toys, books, movies, and parental comforting. Similarly, toys, movies, access to caregivers, reading stories or no distraction at all, were the choice of distraction activities offered to children in the control group in the study by Kipping et al. (2012).

Type of VR used in experimental groups.

All of the trials provided multisensory (auditory, tactile and visual) feedback, although, they varied in the types of VR equipment and the level of patients' immersion into the virtual world. Two studies provided sensory input of VR experience through HMD, headphones and

joystick (Hua et al., 2015; Kipping et al., 2012). Both studies used of-the-shelf VR system with an 800x600 resolution HMD and a personal computer (see Figure 2,).

Figure 2. *VR equipment - eMagin, Z800 3D Visor (Kipping et al.,2012; Hua et al.,2015).*

The study by Das et al. (2005) utilised a personal computer, HMD with 800x600 video resolution, and inbuilt tracking system that allowed interaction inside the virtual environment by moving head in various directions. A decoder and a mouse were added to be used as a trigger. Figure 3 shows detailed representation of the VR system used in this study.

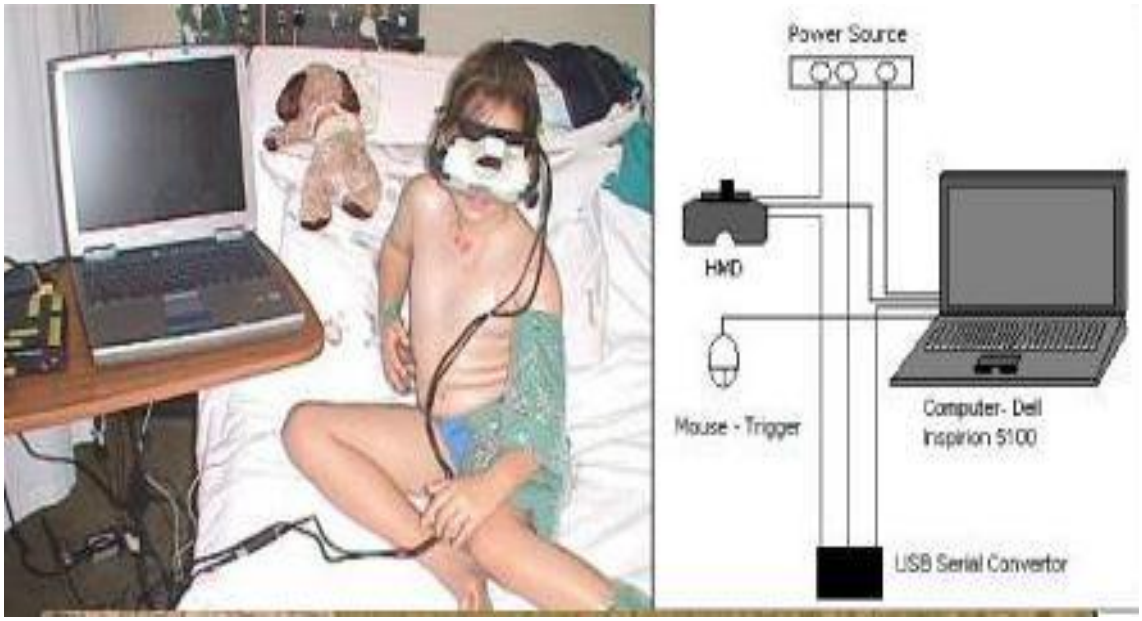

Figure 3. *VR Equipment - IOGlasses with Intersense IS300 (Das et.al,2005).*

A study by Mott et al. (2007) used augmented reality (AR) device instead of VR. The difference between AR and VR is that AR adds digital elements to a physical world instead of implying an immersion into computer-generated world with complete isolation from the physical surroundings. Although this medium does not provide a complete immersion, it still relies on multisensory input (audio, visual, and tactile) and therefore, was included in this systematic review. AR system comprised of an LCD screen with 600x800 resolution that was connected to a computer. The system was operated by inserting plastic figurines into the camera mounted on the screen (Figure 4).

Figure 4.*Augmented Reality (AG) Equipment (Mott et al.,2007).*

As shown in Figure 5, the VR intervention in the study by Jeff et al. (2014) was delivered using a custom-built tripod device with mounted 80-degree field-of-view VR helmet. Audio input was delivered by high quality “external sound cancelling” headphones with interactivity provided by an orbit trackball. Delivering VR through a stationary system instead of head-mounted device allowed the use of VR among patients who had suffered burns to their head.

Figure 5. *VR Equipment - Kaiser Optics SR80a (Jeffs et al.,2014).*

As demonstrated in Figure 6, an immersive VR experience in the study by Schmitt et al. (2010) was created using a stationary computer with attached HMD with 1024x1280 resolution, built-in motion sensing system with 6-degrees-of- freedom tracker attached, and with at least 50° diagonal field of view that is completely blocked off the real world around a navigator.

Figure 6. *VR Equipment - the VR-1280 (Schmitt et al., 2010).*

The study by Gold et al. (2006) used a high-performance HMD with 800x600 resolution, with a 3-degrees-of-freedom tracker attached. A multisensory immersive experience was provided via tactile and auditory feedback that was provided by the navigation via Logitech rumble pad and headphones (see Figure 7).

Figure 7. *VR Equipment - 5DT HMD 800 (Gold et al., 2006).*

Statistical Results of the Selected Studies

A summary of the statistical data of the selected studies is represented in Table 3. The lead researcher developed an Excel data extraction sheet, where the original extracted raw data was recorded.

Table 3. Standard Deviation, Standard Error, and Effect sizes for Control and VR groups in the Selected Studies.

Author	NC	NE	MC	ME	SD cont	SD Ex	SD pooled	Standardised mean difference	Standard Error
Das et al.,2005	7	7	4.1	1.3	2.9	1.8	2.41	-1.16	0.64
Gershon et al.,2004	22	22	10.16	9.35	1.9	1.5	1.71	-0.47	0.26
Gold et al.,2006	10	10	2.4	1.8	1.84	2.4	2.14	-0.28	0.48
Hua et al.,2015	32	33	3.07	1.92	1.66	1.59	1.63	-0.71	0.20
Jeffs et al.,2014	10	8	3.84	2.87	1.16	1.38	1.28	-0.76	0.30
. Kipping et al.,2012b	21	20	4.2	2.9	3.2	2.3	2.79	-0.47	0.44
Mott et al.,2007	22	20	5.38	2.81	0.58	0.89	0.75	-3.43	0.12
Schmitt et al.,2010	54	54	4.1	2.9	0.5	0.45	0.48	-2.53	0.05
Wolitzky et al.,2005	10	10	8.3	4.9	2.41	0.99	1.84	-1.85	0.41

NC= Number of Patients in Control Group; NE= Number of Patients in Experimental Group; MC= Mean Scores in Control Group; ME= Mean Scores in Experimental Group; SD cont=Standard Deviation Control Group; SD EX= Standard Deviation Experimental Group; SD pooled= Standard Deviation Pooled.

Quality Assessment Using PEDro Rating Scale.

Assessment of validity strength of nine selected trials delivered scores ranged from 6/11 to 8/11. The scores described by the Physiotherapy Evidence Database as being of high value range between 6 to 11 on the PEDro scale, decent quality equals PEDro scores 4 to 5, and the poor quality is PEDro score ≤ 3 (PEDro, 1999). Thus, the overall scores of the selected studies described their quality as high. The results of the assessment are presented in Table 4.

Table 4. Quality Assessment Using PEDro Rating Scale.

Criteria	*Hua et al. (2015)*	*Gershon et al. (2004)*	*Gold et al. (2006)*	*Wolitzky et al. (2005)*	*Das et al. (2005)*	*Jeffs et al. (2014)*	*Kipping et al. (2012)*	*Schmitt et al. (2010)*	*Mott et al. (2007)*
1. Eligibility Criteria was specified	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Random Allocation	✓	✓	✓	✓	✓	✓	✓	✓	✓
3. Concealed Allocation	✓	✓				✓	✓	✓	
4. Baseline Similarity	✓		✓		✓		✓	✓	✓
5. Blinding of Subjects						✓			
6. Blinding of Therapists									
7. Blinding of Assessors					✓				
8. Min 1 key outcome from min 85% of subjects	✓	✓	✓	✓		✓	✓	✓	✓
9. Intention-to-treat Analysis	✓	✓	✓	✓	✓		✓	✓	✓
10. between-group statistical comparisons for at least one key outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓
11. Point & Variability measurements	✓	✓	✓	✓	✓	✓	✓	✓	✓
Total PEDro score	**8**	**7**	**7**	**6**	**7**	**7**	**8**	**8**	**7**

The first criterion of the scale was the eligibility of the participants to be included in the study. This criterion was satisfied because all the selected studies described their source of subjects and the list of criteria describing the eligibility of each participant to be included in the study. The detailed description of the eligibility criteria for the participants was presented in the ‘Inclusion/Exclusion Criteria’ section of this review.

Based on the criteria two and three of the scale, studies were required to provide a random and concealed allocation of the participants to avoid a biased distribution of participants’ characteristics. The precise method of randomisation and concealed allocation

had to be described. All nine studies fulfilled the requirement for random allocation, however, only five studies provided concealed allocation.

Based on the fourth criterion, each study had to ensure baseline similarity between groups by providing at least one measure of the severity of the treated condition and at least one key outcome measure that was different. This criterion aimed to minimise possible imbalance between groups' baseline characteristics that may bias the outcome of the treatment. As demonstrated in Table 4, only six studies fulfilled the requirement of this criterion.

Criteria five to seven required studies to provide blinding of the participants, therapists, and assessors in the group allocation process. Clearly, none of the studies provided blinding of the therapists due to the invasive nature of the treatment. Trial by Jeffs et al. (2014) blinded their participants, and Das et al. (2005) provided blinding of an assessor.

Based on criterion eight (minimum 1 key outcome from minimum 85% of subjects), the studies had to report the number of participants initially allocated to groups, and the number of the participants from whom a key outcome measure was obtained. In the trials where the outcomes were measured at several points of time, the conditions of this criterion were satisfied only if at least 85% of all the participants initially allocated to groups reported at least one key outcome measure at least at one of those points of time. Eight studies, with the exception of a study by Das et al. (2005) fulfilled these requirements.

Criterion nine (intention-to-treat analysis) was satisfied if a study stated that all the subjects received treatment as per their experimental or control group allocation. In cases where certain subjects were not treated as per initial group allocation, a study had to provide analysis of data based on how each subject should have been treated in accordance with their initial group allocation. A trial conducted by Jeffs et al. (2014) reported the total number of

enrolled participants who met eligibility criteria. Two of those participants withdrew or had their treatment postponed. The study did not inform any follow-up steps regarding these missing outcomes and therefore, did not satisfy this criterion.

Studies had to provide a statistical comparison between experimental and control groups for at least one key outcome measure to satisfy criterion ten. Finally, yet importantly, trials had to provide a measure of a size of the treatment effect as per criterion 11. All the selected studies satisfied these criteria.

The detailed description of each criterion is presented in Appendix 1. The primary researcher analysed each of the nine selected studies according to the criteria of the scale. Two supervisors checked the accuracy of the evaluation, and inter-rater agreement about the validity of each study has been met.).

Synthesis of Results

Following the method of Wolf (1986), a raw effect size was calculated for each of nine studies in the subgroup analysis. The effect sizes were corrected for small sample bias using Hedges's g (Hedges & Olkin, 2014). A Forest plot for the effect sizes is provided in Table 5.

Table5. Forest Plot for the Individual and Pooled Effect Sizes.

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Das et al.,2005	-1.09	0.60	0.36	-2.26	0.09	-1.81	0.07
Gershon et al.,2004	-0.46	0.26	0.07	-0.96	0.04	-1.81	0.07
Gold et al.,2006	-0.27	0.46	0.21	-1.17	0.63	-0.58	0.56
Hua et al.,2015	-0.70	0.20	0.04	-1.09	-0.31	-3.55	0.00
Jeffs et al.,2014	-0.72	0.29	0.08	-1.28	-0.16	-2.53	0.01
Kipping et al.,2012b	-0.46	0.43	0.19	-1.31	0.38	-1.07	0.29
Mott et al.,2007	-3.37	0.12	0.01	-3.60	-3.13	-28.58	0.00
Schmitt et al.,2010	-2.51	0.05	0.00	-2.61	-2.41	-50.60	0.00
Wolitzky et al.,2005	-1.77	0.39	0.15	-2.54	-1.00	-4.51	0.00
Random-Effect model	-1.30	0.38	0.14	-2.04	-0.56	-3.45	0.00

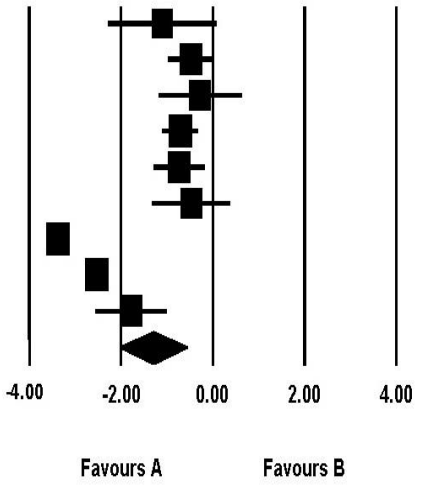

Table 5 demonstrated individually adjusted effect sizes and the pooled Effect Size. Based on the Cohen (2013) guidelines, three studies (Gershon et al., 2004; Gold et al., 2006; Kipping, Rodger, Miller, & Kimble, 2012a) showed small effect sizes; two studies (Hua, Qiu, Yao, Zhang, & Chen, 2015; Jeffs et al., 2014) fell into a medium-range, and the remaining four studies demonstrated a large effect size. The difference between groups was statistically significant for seven out of nine studies with a p-value <.05 and a confidence interval (CI) of 95%. With small effect sizes and p>.05, studies by Gold (2006) and Kipping (2012) did not demonstrate significant difference between VR groups and those receiving a standard distraction.

The pooled effect size of -1.30 was calculated using random-effects model. It fell into an extensive range. This result suggested that the average participant in the experimental group receiving some form of VR distraction experienced noticeably and consistently lower levels of pain and distress during a painful medical procedure.

Homogeneity analysis showed that the sample of nine effect sizes was heterogeneous (Q=287.23, I-squared=97.22, df=8 with a p-value <.05), and the magnitude of true heterogeneity was substantial. Cumulative results for meta-analysis statistics of the selected studies are presented in Table 6.

Table 6. Cumulative Meta-Analysis Statistics.

Model		**Effect size and 95% confidence interval**					**Test of null (2-tail)**			**Heterogeneity**		
Model	*N of studies*	*Point estimate*	*Standard error*	*Variance*	*Lower limit*	*Upper limit*	*Z-value*	*P-value*	*Q-value*	*df (Q)*	*P-value*	*I-squared*
Fixed	9.00	-2.39	0.04	0.00	-2.50	-2.30	-56.01	0.00	287.23	8.00	0.00	97.22
Random	9.00	-1.30	0.38	0.15	-2.04	-0.56	-3.45	0.00				

These results indicated that the large percentage of variation between the studies (I-squared=97.22) was due to heterogeneity rather than just a chance, and was attributed to such variables as type of medical intervention, type of distraction in control groups, the sample size in each study and type of VR distraction.

Subgroup Variables in VR Distraction

As suggested byWang and Ware (2013), the subgroups for this analysis were determined through their baseline characteristics defined by the eligibility criteria of this review, and described in Table 2 of the ‘Study Characteristics’ section. Several study characteristics, such as type of medical intervention, type of pain relief in control groups and the sample size in each study were determined as variables that may increase the power of the Q statistic.

Eight out of nine selected studies used fully immersive VR as their method of distraction in experimental groups, and the study by Mott et al. (2007) used AR. Although the difference

between the types of VR distraction (fully immersive vs. augmented reality) is a study characteristic that may explain the variance between the studies, it was not chosen as one of the variables for the subgroup analysis, because the minimum amount of studies recommended for each categorical subgroup variable must be more than two. This is the minimum number required to yield any clinically meaningful results in detecting an association between effect size and subgroup variance (Fu et al., 2011).

Type of medical procedure.

Studies by Gershon et al. (2004) and Wolitzky et al. (2005) evaluated the effectiveness of the VR as a distractor during port access for intravenous medications procedures in oncology patients. The other five studies were working with children with burn injuries. Hua et al. (2015) were using VR as a method of pain management during dressing changes in children with chronic wounds on lower limbs, and Gold et al. (2006) worked with children during IV placement for magnetic resonance imaging (MRI). All the studies were divided into two main types. Type 1 was attributed to the procedures undertaken with children who required IV placements related to oncology or MRI preparation. Type 2 included dressing changes in children with chronic wounds or burn injuries.

Table 7. Sub-Group Analysis of the Subgroup Variables (Type of Medical Procedure).

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-0.8641	0.6162	-2.0719	0.3436	-1.4	0.1608
Type of medical procedure: 2	-0.7082	0.75	-2.1782	0.7618	-0.94	0.345

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 0.89, df = 1, p = 0.3450
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.9878, Tau = 0.9939, I^2 = 96.65%, Q = 209.14, df = 7, p = 0.0000

Total between-study variance (intercept only)
Tau^2 = 1.1865, Tau = 1.0893, I^2 = 97.15%, Q = 280.97, df = 8, p = 0.0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.17

Type of medical procedure: 1= IV placements related to oncology or MRI preparation; Type of medical procedure: 2= dressing changes in children with chronic wounds or burn injuries

The results for the differences between types of medical procedures used in the selected studies yielded the results displayed in Table 7. The coefficient for the predicted impact of type of medical procedure on study effect size was not statistically significant.

As demonstrated in Table 7, the test of within-groups variance showed no statistical difference (Q = 0.89, df = 1, p = 0.3450). The goodness of fit test demonstrated that the value of Q was higher than it would be expected based on within-study sample error; and 96.65% was the amount of the observed variance that reflected real differences in study effects (I^2 = 96.65%, Q = 209.14, df = 7, p = 0.0000). As shown in Figure 9, the proportion of the total between-studies variance explained by the type of painful medical procedure was 17%. This test demonstrated that there was no significant interaction between the magnitude of effectiveness of VR distraction and types of medical procedures in the selected studies.

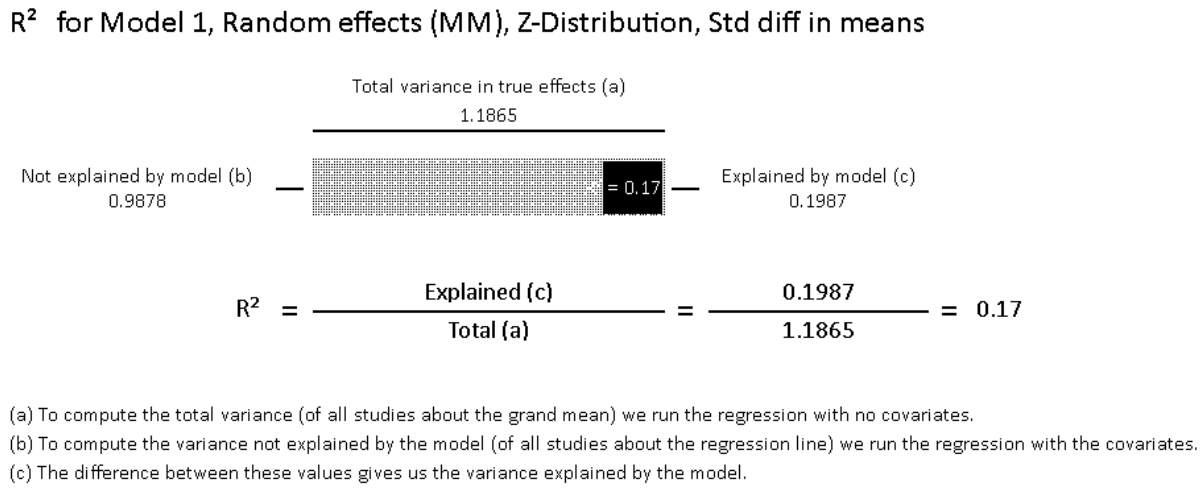

Figure 8. *Proportion of Variance Explained by Type of Medical Procedure.*

Type of pain relief in the control group.

Six studies out of nine used some kind of pharmacologic analgesia during medical procedures, and three studies utilized non-pharmacological distraction. All of the studies were divided into two main types based on the type of pain relief used in control groups. All of the studies that used some kind of pharmacological analgesia were assigned to Type 1. Type 2 included all non-pharmacological methods of distraction.

Table 8. Sub-Group Analysis of the Subgroup Variables (Type of Intervention in CG).

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-0.5567	0.4849	-1.5072	0.3938	-1.15	0.251
Type of intervention in CG	-1.2363	0.5988	-2.4099	-0.0627	-2.06	0.039

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
4.26, df = 1, p = 0.0390

Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.6111, Tau = 0.7817, I^2 = 94.15%, Q = 119.67, df = 7, p = 0.0000
p = 0.0000

Proportion of total between-study variance explained by Model 2
R^2 analog = 0.48

The results for the differences between types of analgesia used in control groups yielded the results displayed in Table 8. The coefficient for predicted impact of type of pain relief applied in CGs was -1.2363, with standard error 0.5988, and Z-value -2.06 with $p<0.05$. This result tells us that pharmacological analgesia was probably more effective than other means of distraction in the control groups.

The goodness of fit test was statistically significant and showed that the Q-value was higher than would be expected in within-study sample error, and 94.15% of the observed variance could be explained by between-studies differences (I^2 = 94.15%, Q = 119.67, df = 7, p = 0.0000, two-tailed). This test showed that the effect size for VR distraction was significantly higher in those trials that used non-pharmacological analgesia in their CGs. As demonstrated in Figure 9, the total proportion of the variance in true effect sizes between the studies explained by the type of analgesia used in the control groups was 48%.

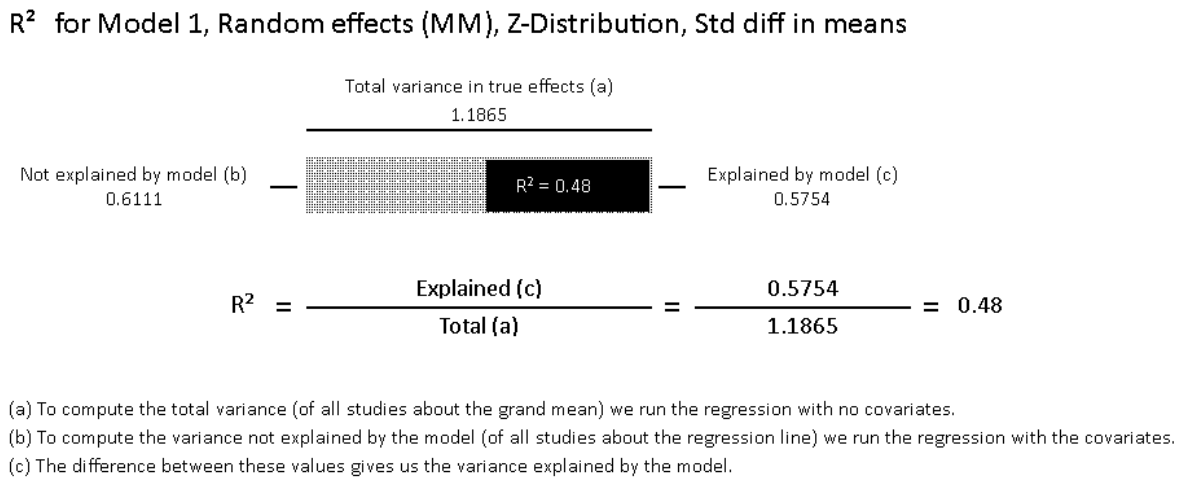

Figure 9. *Proportion of Variance Explained by Type of Intervention in CG.*

Sample size in each study.

Sample sizes used in the selected studies were quite diverse, varying from 14 participants (Das, Grimmer, Sparnon, McRae, & Thomas, 2005) to 108 in the study by Schmitt et al. (2010). The results for the differences between sample sizes of the selected trials are displayed in Table 9. The coefficient for predicted impact of the study size on its effect size was not statistically significant, meaning that there was no significant relationship between a study size and the effectiveness of VR distraction in that study. The total variance in true effect sizes between the studies explained by the study size was 0%.

Table 9. Sub-Group Analysis of the Subgroup Variables (Study Size).

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-0.7609	0.958	-2.6386	1.1167	-0.79	0.427
study size	-0.0131	0.0188	-0.05	0.0237	-0.7	0.4846

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 0.49, df = 1, p = 0.4846
Goodness of fit: Test that unexplained variance is zero
Tau² = 2.4720, Tau = 1.5723, I² = 97.36%, Q = 264.71, df = 7, p = 0.0000

Proportion of total between-study variance explained by Model 1
R² analog = 0.00 (computed value is -1.08)

Figure 10 demonstrated that the proportion of total between-studies variance explained by the sample size of study was 0%.

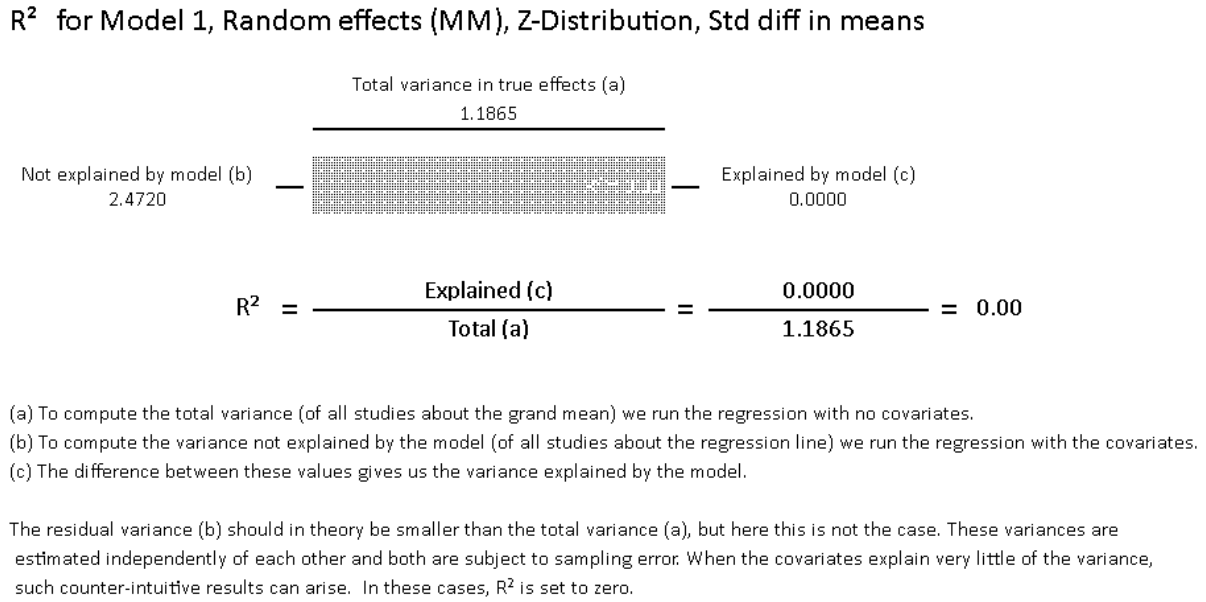

Figure 10. *Proportion of Variance Explained by Study Sample Size.*

Analysis of Publication Bias.

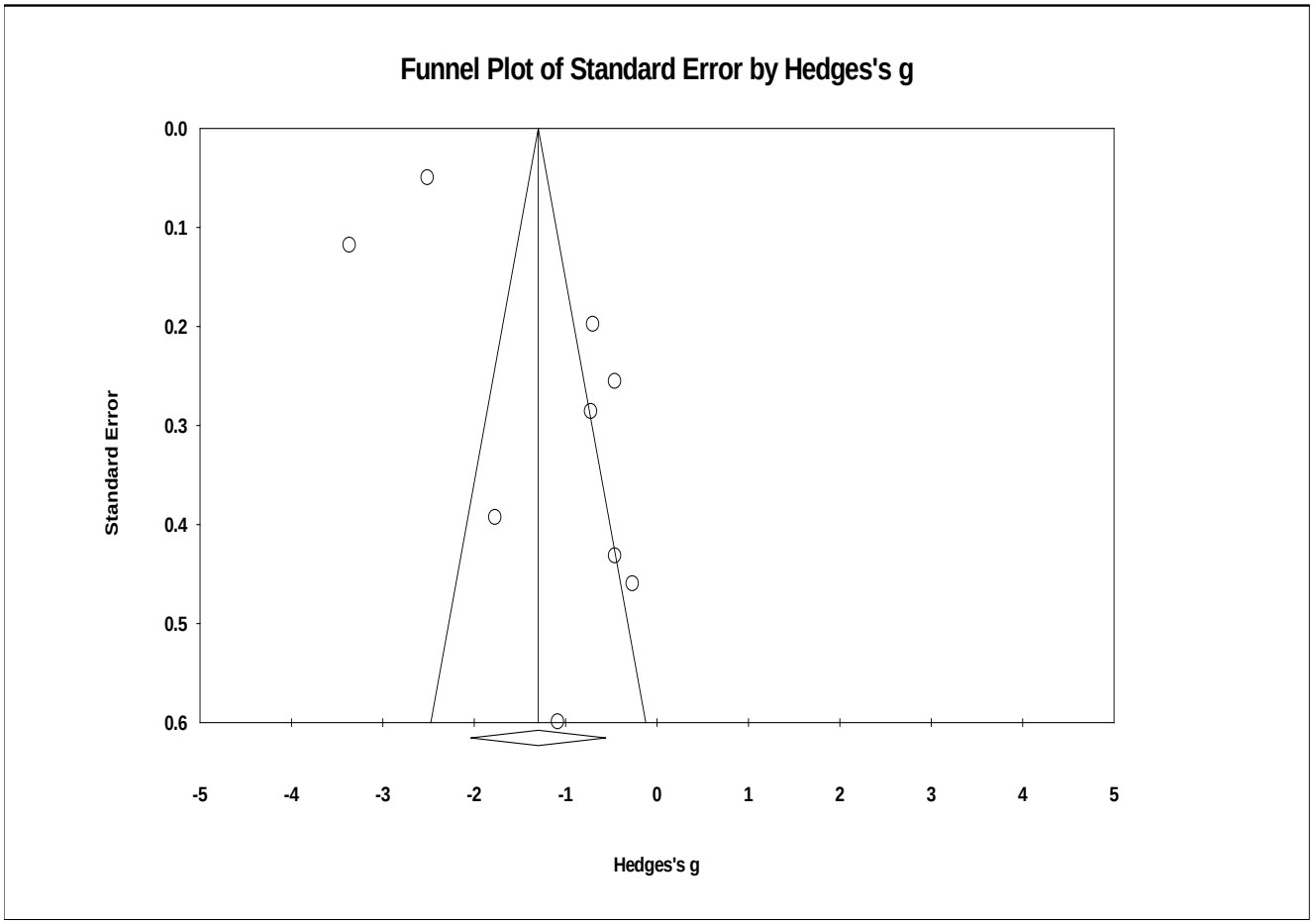

Figure 11. *Funnel Plot of Publication Bias by Hedges's g.*

As demonstrated by Figure 11, the studies in this analysis did not fit within the funnel, nor was the roughly similar number of effect sizes located on both sides of the mean effect size in the middle of the funnel plot. This suggested that some kind of publication bias or a large amount of heterogeneity between the studies was present. To address the issue of possible publication bias, another test, called Orwin's fail-safe N, was applied (Orwin, 1983). The fail-safe N is the number of studies with 0 effect size that would be required to bring down a large mean effect size to an insignificant level. Hedges's g in the observed studies was

-1.30. The criterion for a 'trivial' Hedges's g was established at -0.20. To reduce the current mean weighted effect size to a small effect size of -0.2, additional 50 studies with an effect size zero would be needed.

Discussion

The results of this systematic review demonstrated that overall, VR was more effective as a pain and anxiety control measure than traditional pain management techniques when used during painful medical procedures among the paediatric population. All nine studies showed individual effect sizes in favour of VR as demonstrating an overall reduction in anxiety and pain in the experimental groups vs. control groups, with a statistically significant total effect size of -1.30. The total effect size compared favourably with other psychological interventions that were used among paediatric populations for the management of pain and anxiety during painful medical procedures.

For instance, Alhani, Shad, Anoosheh, and Hajizadeh (2010) obtained an effect size of only -.2 in their study investigating the effectiveness of the programmed distraction in adolescents during venipuncture procedures. Similarly, the study by Ramírez-Carrasco et al. (2017) investigated the effectiveness of hypnosis in combination with conventional behavioural pain management techniques during paediatric dental procedures. Results of this study demonstrated only a marginal statistical difference ($p = 0.05$) in the heart rate between control (application of conventional behaviour management techniques alone), and experimental (hypnosis intervention) groups, being lower in the hypnosis group. No statistical differences were found in pain and anxiety levels between experimental and control groups. Likewise, a meta-analysis of the effectiveness of distraction during needle-related painful medical procedures in adolescents conducted by Birnie et al. (2014) yielded an effect size of -.44.

Results also demonstrated there was significant heterogeneity between the studies, and subgroup analysis suggested the treatment effect was not consistent and varied significantly across the subgroups. Variables that influenced treatment effect across the studies were determined as a type of medical procedure, method of pain management applied in the control group and the size of the study. The largest proportion of the variance across study subgroups (48%) was attributed to the type of analgesia used in control groups during painful medical procedures. This result demonstrated that pharmacological pain relief methods were more effective than non-pharmacological, suggesting that the effect size was influenced by the difference in outcome across pharmacological and non-pharmacological subgroups of the trials. Studies that used non- pharmacological analgesia in CG, demonstrated greater effectiveness compared to those that used standard pain relief.

Other covariates did not produce any statistically significant results, meaning that there was no observable relationship between treatment effect and study size or the type of medical procedure used in a trial. Given this conclusion was based on a small number of studies, further trials are required to determine outcomes that are more definite.

Overall, the results of this systematic review suggested that the application of VR during painful medical procedures in children and adolescents could be at least as effective as other popular non-pharmacological methods of pain intervention used in modern hospital settings.

Our results mirror the existing literature on the use of VR in adult patients undergoing painful medical procedures in various medical settings (Dascal et al., 2017; Malloy & Milling, 2010).

Clinical Implications

A strong factor that favours use of VR in various hospital settings is its decreasing costs and increasing customizability and flexibility of the gaming context. VR has been known since the 1960s and research about its application has become widespread since 1980

(Coburn, Freeman, & Salmon, 2017). Initially, the VR hardware was bulky, expensive and had a low resolution. However, the recent five years have generated much more user-friendly and affordable VR software and hardware that can be used in numerous applications. As an effective pain management tool, it can be integrated into various medical procedures that include invasive procedures and pain rehabilitation (Dascal et al., 2017).

VR can be used in conjunction with pharmacological analgesia. For example, traditional pharmacological methods of pain management in burnt children are often insufficient and cannot cope with the intensity of the pain caused by burn wounds (Das et al., 2005). VR can be a valuable distraction tool that can be used in combination with standard pharmacological analgesia during burn wounds care and other aversive medical procedures (Chan, Chung, Wong, Lien, & Yang, 2007; Das et al., 2005; Steele et al., 2003). The study conducted by Das et al. (2005) investigated the effectiveness of VR as a pain management technique in children with acute burn injuries. Children in the trial acted as their own controls. They were administered pharmacological analgesia throughout the duration of 11 trials, and in addition to it they used VR half of the time. The results for the application of pharmacological analgesia alone were significantly lower compared to the results of the combined application of analgesia and VR. As a safe, non-pharmacological tool, VR can become an invaluable addition to standard treatment of pain in children.

In addition, VR can be used with other non-pharmacological methods of pain management, such as hypnosis. It can also become an effective alternative to hypnosis for those patients who score low on the personal level of suggestibility.

Limitations

This systematic review has a number of limitations. The first is that the definition of VR in the selected studies was variable. As demonstrated in Figures 2-8, the devices used in the

studies differed in their technical descriptions. Although all of them delivered an auditory and visual experience of presence in a 3D-environment, the mechanism of providing this experience varied greatly. For example, Mott et al. (2007) used AR equipment comprised of a screen with buttons; Jeff et al. (2014) used a stationary device with a joystick; other studies used HMD (Das et al., 2005; Kipping et al., 2012a).

A second limitation was that the indicators of pain (intensity, tolerance), measured outcomes (pain and anxiety or just pain), and pain measurement intervals were averaged across the studies, meaning that potential differences between measurements in individual studies could be concealed. However, it was not feasible to conduct a comparative analysis of each individual

measure because not all of them were included in each selected study.

A third limitation was that because the scope of this work was limited to studies from peer-reviewed journals. Without unpublished research and conference presentations, the overall efficacy of the VR method of distraction could be overestimated. This so-called file drawer effect means that studies that often fail to reach significance remain unpublished while creating a tendency for studies with statistically significant results to be preferentially published in peer-reviewed journals. However, Orwin's fail-safe analysis conducted for this report, indicated that an additional 50 studies with an effect size 0 would be needed to overestimate the efficacy of VR. It is unlikely that an additional 50 unpublished studies that demonstrated no effectiveness of VR exist.

A fourth limitation of this systematic review was a possible overestimation of the results presented by the studies due to an English language bias. The studies selected for this review were English language only due to insufficient language resources, time, and funding for professional translation necessary to include studies that were not published in English.

Studies with negative findings affected by this bias often get a preferred publication in foreign language journals making incorporation of such studies less likely (Orwin, 1983).

Unfortunately, there are also some limitations associated with the use of VR during painful medical procedures. First, the number of children who can use the device is limited because of their susceptibility to head and hands injuries and to the high severity of burns (Bartlett, 2002). Research has shown that children suffer from increased severity of burns compared to adults because of their thinner epidermis. Their head to body ratio is also more significant than in adults, which makes them more susceptible to head injuries (Mohan, 1996). It may be problematic or even impossible to use an HMD from the VR equipment in children with severe facial burns or head injuries. It could also be difficult to use a system with a joystick in children with hand burns or other hand injuries (Das et al., 2005).

Secondly, VR may have negative side effects including motion sickness or nausea. This factor must be taken into account when using VR in paediatric patients during certain medical procedures that can induce nausea and vomiting, such as chemotherapy, and should be factored in when determining whether this type of distraction is suitable for a particular patient (Miller, Rodger, Kipping, & Kimble, 2011; Tyc, Mulhern, Jayawardene, & Fairclough, 1995).

Another factor to consider in the application of VR is its sustained efficacy. Studies suggested that standard methods of pain management might lose their novelty effect. As a result, their effectiveness can decrease over time (Rutter, Dahlquist, & Weiss, 2009). The sustainable maintenance of the treatment effects is essential because certain medical procedures require multiple painful treatments. The study by Rutter et al. (2009) addressed the sustainability of VR analgesia in adults, and the results indicated the sustained efficacy over a period of 8 weeks of treatments. This is a promising result in terms of the effectiveness

of VR; however, no similar studies were conducted with the paediatric population, and thus, the sustainability of VR in children is yet to be addressed.

Future Research

Although this systematic review demonstrates that VR may serve as an effective pain and anxiety management technique in children during painful medical procedures, it also highlights the gaps in the research concerning this type of distraction. To date, most research in this area was conducted utilising case study or within-subjects designs, which included very small sample sizes. To evaluate the efficacy of VR as a pain and anxiety management method further, more randomised control trials with large sample sizes are needed.

Equally, more studies on the use of VR in various medical settings for the paediatric population are needed. For instance, the use of VR distraction to alleviate anxiety and discomfort prior to magnetic resonance imaging (MRI) procedures remains an unexplored area of research. VR as a treatment method in adolescents with substance abuse disorders is another example that requires further research. VR could help young people to increase their motivation to quit smoking or use drugs or keep them from returning to substance abuse. For instance, one study conducted by Caponnetto, Maglia, Lombardo, Demma, and Polosa (2019) compared various motivational stimuli to help young adults to quit smoking. Their results suggested that the VR application could increase motivation to quit smoking among adolescents who did not show such intent prior to VR exposure.

This systematic review did not address the difference in effect size between off-the-shelf devices and customised systems. The results from the studies by Das et al. (2005) and Kipping et al. (2012) showed more significant pain reduction scores attributed to the customised VR applications. These results could guide future research in investigating the relationship between the specific age, gender, and the type of VR games used during medical procedures.

The role of motivational relevance in enhancing the effectiveness of this type of pain control also remains an unexplored area of research. Previous research demonstrated that the effect of distraction techniques might be improved by motivational relevance, and, as a result, higher pain reduction scores can be achieved (Verhoeven et al., 2010). Customising VR software to improve the motivational relevance of a patient could increase the distracting effect of this pain control method.

Finally, variables, such as the quality of screen resolution and the types of VR devices were not controlled in this systematic review. Future research should study the role of these factors in determining what specific devices can produce the best outcomes in managing pain during painful medical procedures.

Conclusion

VR combines innovative computer technology with the time-proven principle of using distraction to reduce pain. The systematic review of nine controlled studies demonstrated that VR distraction was a more effective method of pain management than standard methods of analgesia. These results suggested that clinicians should feel confident utilising it with their paediatric patients, especially those who do not respond well to other interventions. Further research is recommended, to determine which variables moderate the effectiveness of VR as a distractive method for children undergoing painful medical procedures.

Appendices

Appendix 1. PEDro scale.

PEDro scale

1.	eligibility criteria were specified	no ❑ yes ❑ where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no ❑ yes ❑ where:
3.	allocation was concealed	no ❑ yes ❑ where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no ❑ yes ❑ where:
5.	there was blinding of all subjects	no ❑ yes ❑ where:
6.	there was blinding of all therapists who administered the therapy	no ❑ yes ❑ where:
7.	there was blinding of all assessors who measured at least one key outcome	no ❑ yes ❑ where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no ❑ yes ❑ where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no ❑ yes ❑ where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no ❑ yes ❑ where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no ❑ yes ❑ where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (*Verhagen AP et al (1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41*). The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or "generalisability" or "applicability" of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the "validity" of a study's conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the "quality" of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

Last amended June 21st, 1999

Notes on administration of the PEDro scale:

All criteria	**Points are only awarded when a criterion is clearly satisfied.** If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.
Criterion 1	This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.
Criterion 2	A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.
Criterion 3	*Concealed allocation* means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was "off-site".
Criterion 4	At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups' outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.
Criteria 4, 7-11	*Key outcomes* are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.
Criterion 5-7	*Blinding* means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be "blind" if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.
Criterion 8	This criterion is only satisfied if the report explicitly states *both* the number of subjects initially allocated to groups *and* the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.
Criterion 9	An *intention to treat* analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.
Criterion 10	A *between-group* statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a "p" value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.
Criterion 11	A *point measure* is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. *Measures of variability* include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.

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